Remarks

Applicants note with appreciation the withdrawal of finality of the previous Office Action pursuant to 37 CFR 1.114. Applicants further note with appreciation the Examiner's withdrawal of some of the rejections and objections contained in the previous Office Action.

In accordance with the Examiner's helpful suggestions, the Applicants have amended the Specification concerning Hsu et al. to properly reflect the appropriate reference year, which now reads, "April 1992". The current Office Action asserts that the Applicants most recent amendment to the Specification had deleted the year in the reference of Sun et al. However, Applicants respectfully submit that a study of both the clean and marked-up versions of the Applicants previous response dated January 8, 2003 demonstrates that the amended Specification did not delete the year of reference. (copy enclosed). Specifically, the clean and marked-up versions read "Sun, J., M. Inouye, and S. Inouye, **1991**, Association of retroelement with a P4'-like cryptic prophage (retronphage ϕ R73) integrated into the selerocystyl tRNA gene of Escherichia coli. J. Bacteriol. 173:4171-4181." Applicants further submit that the previous Amendment to page 11, lines 17-22 had not deleted reference to the sequences in the drawings. Specifically, and as can be seen in the enclosed clean copy and marked-up versions of the Amendment dated January 8, 2003, SEQ ID NO's 32-38 are clearly delineated. Consequently, it is respectfully submitted that SEQ ID No's 32-38 do not need to be re-inserted.

In accordance with the Examiner's helpful suggestions the Applicants have amended Claim 1 to clear up minor informalities. Applicants note, however, that SEQ ID NO: 1 refers to both a nucleic acid and amino acid sequence.

Claim Rejections – 35 U.S.C. § 112

Claims 1, 2, 4-6, 12 and 17 have been rejected under 35 U.S.C. § 112, second paragraph.

In accordance with the Examiner's helpful suggestions, the Applicants have amended Claim 1 to clarify the recitation of (SEQ ID NO: 1). Further, the Applicants have removed the phrase "substantially homologous amino acid sequence." The Applicants submit, however, that it is well understood in the art that conservative substitutions may be made to a sequence without changing either structural or function of the polypeptide. Such conservative substitutions are generally result when one amino acid of like hydrophobicity, charge and orientation is substituted with another amino acid having the same properties.

Applicants have amended Claim 6 to clarify the sequence that Claim 6 refers to.

Turning now to a consideration of Claim 15, the Applicants have provided additional structural features along with the structural features already contained in Claim 15 to demonstrate that the Applicants were in possession of the claimed reverse transcriptase. Support for this claim amendment can be found in Figs. 5 and 14 of the specification and the sequence listing for SEQ ID No. 11-24 and 32-38, which illustrate the conserved YXDD box contained within the various reverse transcriptases identified in the specification. Given the inclusion of these sequences and the respective location of their YXDD box, as delineated in Figs 5 and 14, one skilled in the art would readily recognize that the Applicants were in possession of a prokaryotic reverse transcriptase having a YXDD box conserved among the various prokaryotic organisms.

As a result, the Applicants respectfully submit that Claim 15 clearly describes all the necessary structural and functional features of bacterial reverse transcriptase, so that a skilled artisan would clearly recognize the Applicants were in possession of the claimed genus.

Claim Rejection Under 35 U.S.C. § 102

Claims 1, 2, 5, 6, 8, 10, 15 and 16 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Lim and Maas (Cell 56:891-904, 1989).

Applicants respectfully submit that as a result of the amendments to independent Claims 1 and 15, the rejection is now obviated. Specifically, the Applicant's have removed the reference to "substantially homologous amino acid sequence" in the claims and as a result Lim and Maas fail to teach a 485 amino acid open reading frame.

Claim Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4-8 and 15-17 have been rejected under 35 U.S.C § 103(a) as being unpatentable over either of Inouye et al. (U.S. Patent No: 5,320,958 or U.S. Patent No. 5,434, 070), in view of Rice et al., Xiong et al. and Hsu et al. Applicants respectfully submit that the current application claims benefit of both U.S. Patents '958 and '070. Applicants respectfully submit that inventors' own prior original work can not be cited as part of the prior art to show that the later invention is obvious under § 103, unless the inventors' own work in the form of a patent, printed publication or public use is more than a year before the application for a patent. *In re Pleuddemann,* 15 USPQ2d 1738 (Fed. Cir. 1990); and *In re Jaeger*, 112 USPQ 477 (CCPA 1957). The current application was filed prior to the issuance of the '070 and '958 patents. Specifically, the current application was filed on June 30, 1994, while the '070 and

'958 patents issued on June 13, 1994 ('958 patent) and July 19, 1995 ('070 patent). Consequently, the aforementioned patents did not issue more than one year before the date of the application for patent in the current application. Therefore, the '070 and '958 patents do not qualify as prior art.

Moreover, the Applicants respectfully submit that simply because one skilled in the art may be aware that reverse transciptases could be contained in a bacterial genome, albeit in limited number of genomes, there is no suggestion that one skilled in the art would be able to find the particular reverse transcriptases as described in the Applicants' claims. It would be mere speculation to assert that having knowledge of an unspecified gene coding for a "factor X", and a general method for finding a "factor", that one skilled in the art would necessarily be able to locate a specific and functional "factor X" in a particular genome, characterize it, sequence it, and identify its essential elements. If that were the case, than the isolation and purification of one gene and any steps related thereto would obviate the isolation, and characterization of any related gene in any organism. The aforementioned hypothetical is clearly not the goal of the patent system. If it were, there would be no incentive to further the art in the isolation, characterization and purification of genes which may or may not be contained within a genome of a particular organism, once a single gene from a single source has been characterized.

Turning now to the rejection of Claims 1, 2, 4-6, 8, 15-17 rejected under 35 U.S.C. § 103(a) as being unpatentable over Hsu et al. in view of Lim and Maas, the Applicants respectfully submit that as a result of the claim amendments and the remarks set forth below, the rejection is now obviated. Applicants respectfully submit that Hsu et al. merely indicates the presence of msDNA in *M. xanthus* and *E. coli*. The Applicants, however, submit that

owing to the substantial differences between these two species and their respective reverse transcriptases, one skilled in the art had no motivation to combine the teachings of Hsu et al. with Lim and Maas. Specifically, the Examiner's attention is invited to page 21, lines 14 to page 22, line 27, which states:

> Furthermore, it is of great interest whether the M. xanthus RT is associated with a complex such as virus-like particles such as those found for yeast Ty1 element (Eichinger and Boeke, 1988). In a preliminary experiment, msDNA of M. xanthus exists as a complex with proteins in the cell which sediments as a 22S particle. Characterization of this complex may shed light on questions concerning the relationship between msDNA and retrocomponents as well as the functions of msDNA.
>
> At present, there is no information to support the possibility that msDNA may be a transposable element or an element associated with a provirus (or prophasges). It is important to point out that the RT gene for M. xanthus appears to be as old as other genomic genes for the following reasons: (a) Nine independent natural isolates of M. xanthus from various sites (including Fiji Island and eight different sites in the United States) contained mutually hybridizable msDNA (Dhundale et al., 1985). Since under the same hybridization condition, msDNA-Mx162 did not hybridize with msDNA-Sa163 [which has extensive homology in both DNA and RNA sequences with msDNA-Mx162; Dhundale et al., (1987)], the nine independent strains M. xanthus are assumed to contain almost identical msDNA. (b) The codon usage of the Mx-162 RT is almost identical to those found in other M. xanthus genes (Table 1). M. xanthus is known to have a very high G+C content (70%; Johnson and Ordal, 1968) and as a result, all the genes so far characterized have very high G+C contents at the third positions of condons used; 85.4% for vegA (Komano et al., 1987), 85.7% of ops (Inouye et al., 1983), 87.2% for tps (Inouye et al, 1983), 88.4% for mbhA (Romeo et al., 1986), and 93.9% for sigma factor. The average G+C content of the third positions of the RT codons is highest among these genes (95.5%; Table 1).
>
> In the contrast of E. coli msDNA system including the RT gene is considered to have been acquired much later in the evolution of E. coli. Reasons for this conclusion include: (a) Only four strains out of 89 independent clinical E. coli strains were found to produce msDNA (Lampson et al., 1989b). (b) The codon usage of the E. coli RT is significantly different from the general codon usage of

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> E. coli genes obtained from 199 E. coli genes (Maruyama et al., 1986). In particular, out of 62 arginine codons used in the E. coli RT, 40 (65%) use of AGA or AGG in contrast to 2.7% for the AGA+AGG usage among all arginine codons in 199 E. coli genes (see Table 1). The AGA and AGG codons are the least used codons in E. coli (Maruyama et al., 1986). In addition to AGA and AGG codons, many other codons, GCC and GCG for Ala, CGU and CGC for Arg, CAG for Gln, GGC and GGA for Gly, CAC for His, AUC and AUA for Ile, UUA, CUU and CUG for Leu, UUC for Phe, CCU and CCG for Pro, UCG for Ser, ACC and ACA for Thr, and GUC for Val. (c) Although the E. coli msDNAs share little sequence homology, they all share the key secondary structures of a branched rG residue, a DNA – RNA hybrid at the 3' ends of the msDNA and msdRNA, and stem-and-loop structures in RNA and DNA strands (Lampson et al., 1989b; Lim and Maas, 1989).
>
> **These results clearly demonstrate distinct differences between the msDNA systems of E. coli and M. xanthus.** Myxobacteria are common organisms in soil and are found all over the world regardless of climate, and considered to diverge from their nearest bacterial relatives about $2x10^9$ years ago when the atmosphere became aerobic (see a review by Kaiser, 1986). Since it is reasonable to assume that the M. xanthus RT gene is as old as other genomic genes, the RT gene existed much before eukaryotic cells appeared ($1.4\text{-}0.9 \times 10^9$ years ago). [Emphasis added].

The aforementioned clearly illustrate the distinct differences between the msDNA systems of *E. coli.* and *M. xanthus*. As the Examiner has stated in the office action dated March 26, 2003 the introduction/abstract of Hsu et al. **does not** discuss the homologies of msDNA from *M. xanthus* and *E.coli.* Rather, Hsu et al. shows similarity between *M/ xanthus* and *Aurantiaca.* Hsu et al further describes that the high identity "between the two RTs is unique among all other known bacterial RTs which do not share more than 40% identities." (Hsu et al., page 2385). Accordingly, the teaching of Hsu et al. illustrate the high diversity of RTs among bacterial species. Specifically, Hsu et al. discloses the similarity of RTs in *M. xanthus* and *S. aurantiaca,* but teaches away from the combination of its teaching with a reference related to an *E. coli* RT when it states that only 13% of *E. coli* natural isolates

contain retrons, and those retrons show substantial diversity. (Hsu et al. pg. 2385-2387). Given these significant differences, one skilled in the art had no motivation to combine the teachings of Hsu et al. with Lim and Maas. Furthermore, these differences provide no reasonable expectation of success for the identification of "universal" prokaryotic reverse transciptases.

Applicants further submit that nothing in Hsu et al. refers to the activity of msDNA within *M. xanthus*. Consequently, Hsu et al. is at best an invitation to "try" combining the msDNA systems of *E. coli*. with *M. xanthus*. The "obvious to try" approach in an obviousness rejection was long ago banned by the Federal Circuit.

The case of *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 13 U.S.P.Q. 2d (D. Mas. 1989), Judgment aff'd in part, vacated in part on other grounds, 18 U.S.P.Q. 2d 1014,1016 (Fed. Cir.1991). In *Amgen*, the Federal Circuit noted that an "obvious to try" standard did not offer a reasonable expectation of success for the Applicant. In coming to its conclusion, the Federal Circuit stated that simply because the overall homology of baboon DNA and human DNA was roughly 90%, it was only "obvious to try" the monkey probe. *Amgen, Inc.* 13 U.S.P.Q. 2d at 1018. Realization of the successful use of the monkey probe would not necessarily have been obvious. *Id.* The Court noted that there are many pitfalls in probing and isolating sequences. *Amgen Inc.*, 18 U.S.P.Q. 2d at1022-1023.

In re Vaeck assessed the patentability of an invention relating to a genetically engineered insecticide. *In re Vaeck*, U.S.P.Q. 2d, 1438 (Fed. Cir. 1991). The Court opined that while several references disclosed homologies between bacteria and cyanobacterial, these same references taught differences as well as similarities. In applying the principal of *In re Vaeck*, the differences in retrons as described in Rice et al., and pointed out in this response, clearly

show no suggestion, implicit or explicit, that there would be a reasonable expectation of success in isolating and purifying reverse transcriptases from the highly diverse retrons of a number of bacterial species. Whether a particular combination might be "obvious to try" is not a legitimate test for patentability.

In view of the foregoing, Applicants respectfully submit that the claims are now in condition of allowance, which action is respectfully requested.

Respectfully submitted,

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